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For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: POLYMORPHISMS IN THE HUMAN CYP3A4 AND CYP3A7 GENES AND THEIR USE IN DIAGNOSTIC AND
THERAPEUTIC APPLICATIONS

(57) Abstract: Described are general means and methods of diagnosing and treating the phenotypic spectrum as well as the over-
lapping clinical characteristics with several forms of inherited abnormal expression and/or function of the CYP3A4 and CYP3A7
genes. In particular, polynucleotides of molecular variant CYP3A4 and CYP3A7 genes which, for example, are associated with
insufficient metabolism and/or sensitivity of drugs, and vectors comprising such polynucleotides are provided. Furthermore,
host cells comprising such polynucleotides or vectors and their use for the production of variant CYP3A4 and CYP3A7 proteins
are described. In addition, variant CYP3A4 and CYP3A7 proteins and antibodies specifically recognizing such proteins as well as
transgenic non-human animals comprising the above-described polynucleotides or vectors are provided. Described are also methods
for identifying and obtaining inhibitors for therapy of disorders related to the malfunction of the CYP3A4 and CYP3A7 genes as
well as methods of diagnosing the status of such disorders. Pharmaceutical and diagnostic compositions comprising the above-de-
scribed polynucleotides, vectors, proteins, antibodies and inhibitors by the above-described method are provided. Said compositions

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 00/08570

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68 C12P19/34 C12N9/02 C07K16/18 C12N15/53
A61K38/17 A61P35/00 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WESTLIND A ET AL.: " Interindividual differences in hepatic expression of CYP3A4: Relationship to genetic polymorphism in the 5'-upstream regulatory region." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 259, 27 May 1999 (1999-05-27), page 201-205 XP000907112 the whole document	1-3,13, 14,19, 21,26-33
X	WO 99 13106 A (AXYS PHARM INC) 18 March 1999 (1999-03-18) the whole document	1-9, 12-43
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

1 February 2001

Date of mailing of the international search report

09.05.01

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INTERNATIONAL SEARCH REPORT

Inter national Application No
PCT/EP 08570

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HASHIMOTO H. ET AL.,: "Gene structure of CYP3A4 an adult-specific form of cytochrome P450 in human livers and its transcriptional control" EUR. J. BIOCHEM., vol. 218, 1993, page 585-595 XP000910643 cited in the application the whole document	1-3
X	BEAUNE P.H. ET AL.,: "Isolation and sequence determination of a cDNA clone related to human cytochrom P-450 nifedipine oxidase" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, USA, vol. 83, 1986, pages 8064-8068, XP000907192 cited in the application the whole document	1-3
A	WO 91 10745 A (IMP CANCER RES TECH) 25 July 1991 (1991-07-25) the whole document	1-3, 12-14, 25,27, 35,36, 38,40,41
A	EP 0 759 476 A (OTSUKA PHARMA CO LTD) 26 February 1997 (1997-02-26) the whole document	1-3, 12-14, 25,27, 35,36, 38,40,41
P,X	WO 00 24926 A (LABUDA DAMIAN ;SINNETT DANIEL (CA); HOPITAL SAINTE JUSTINE (CA)) 4 May 2000 (2000-05-04) page 3, line 1 -page 4, line 34 page 5, line 21-32; claims 8-13; example 3	1-3,13, 14,19, 26-33, 36-39
T	SATA F ET AL.,: "CYP3A4 allelic variants with amino acid substitutions in exons 7 and 12: Evidence for an allelic variant with altered catalytic activity" CLINICAL PHARMACOLOGY & THERAPEUTICS, vol. 67, January 2000 (2000-01), page 48-56 XP000910497 cited in the application the whole document	1-3,13, 14,19, 26-33, 36-39

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 97/08570

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	<p>NCBI protein and nucleotide databases. 15-11-2000 AC= AAG32290. CYTOCHROME P450 POLYPEPTIDE 4; CYP3A4. Homo sapiens (Human). Gellner et al., "Genomic organization of the human CYP3A locus: identification of a new, inducible CYP3A gene expressed in the liver, testes and prostate." (unpublished) XP002158367 abstract</p> <p>-----</p>	1-43

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/JP 00/08570

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 28 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1,33,34,37
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-43 all partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,33,34,37

Present claims 1 and 37 relate to an extremely large number of polynucleotide sequence of which only a small fraction could be unambiguously allocated to the CYP3A4 or CYP3A7 variants. In fact, a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those sequences successfully allocated with the help of tables 1-4.

Claims 33 and 34 refer to an inhibitor identified or obtainable by screening compounds able to displace the protein of claim 9 when is bound to a CYP3A4 (or CYP3A7); or contacting such protein with compounds capable of providing a detectable signal in response to drug metabolism. No such compounds are defined in the application. In consequence the scope of said claim is ambiguous and vague, and its subject-matter is not sufficiently disclosed and supported (Art. 83 and 84 EPC).

Therefore, no search can be carried out for such speculative claims whose wording is, in fact, a mere recitation of the result to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M1 (having a nucleotide substitution at position 6004) and a molecular variant of the cytochrome CYP3A7 (having a nucleotide substitution at position 1229), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4 or CYP3A7.

2. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M2 (having a nucleotide substitution at position 13908), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

3. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M3 (having a nucleotide substitution at position 14292), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

4. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M4 (having a nucleotide substitution at position 14304), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

5. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M5 (having a nucleotide substitution at position 21867), its corresponding nucleotide and protein sequences; vectors;

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

6. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M6 (having a nucleotide substitution at position 21896), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

7. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M7 (having a nucleotide substitution at position 22026), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

8. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M8 (having a nucleotide substitution at position 23172), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

9. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M10 (having a nucleotide substitution at position 14323), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

10. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M11 (having a nucleotide substitution at position 14329), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

11. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M12 (having a nucleotide substitution at position 14357), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

12. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M13 (having a nucleotide substitution at position 15753), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

13. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M14 (having a nucleotide substitution at position 20230), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

14. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M15 (having a nucleotide substitution at position 21868), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

15. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M16 (having a nucleotide substitution at position 22041), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

16. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M17 (having a nucleotide substitution at position 23081), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

17. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M18 (having a nucleotide substitution at position 25925), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

18. Claims: 1-43 all partially

A molecular variant of the cytochrome CYP3A4, the so-called M19 (having a nucleotide substitution at position 25958), its corresponding nucleotide and protein sequences; vectors; host cells; antibodies; transgenic non-human animals; pharmaceutical compositions; probes or oligonucleotides thereof as well as methods of diagnostic or identification of inhibitors capable of modulating the activity of a molecular variant of CYP3A4.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EPO/08570

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9913106	A	18-03-1999	AU 9128798 A EP 1012340 A	29-03-1999 28-06-2000
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WO 0024926	A	04-05-2000	US 6183963 B AU 6322299 A	06-02-2001 15-05-2000